Atty. Dkt. No. 065691/0215

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Philippe Msika

Title: COSMETIC METHOD FOR PREVENTING AND/OR TREATING SKIN STRETCHMARKS, AND USE IN DERMATOLOGY

Appl. No.: 09/806,834

Filing Date: 04/05/2001

Examiner: Lauren Q. Wells

Art Unit: 1617

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Philippe Msika, declare that:

1. I am a citizen of France and reside at 1 Petite Place / 78000 Versailles / France.

2. I am the inventor of the above-captioned application, "COSMETIC METHOD FOR PREVENTING AND/OR TREATING SKIN STRETCHMARKS, AND USE IN DERMATOLOGY," Serial No. 09/806,834.

3. I was awarded a Ph.D in cutaneous biology in Paris in 1986, and a Pharmacist Dr. in Tours in 1988.

4. Since 1985, I have been employed in several cosmetic and dermatologic laboratories. I am currently the head of the Research and Development Centre of the Expanscience Laboratory, which is the French and European leader in obstetric and infant skin care.

5. I have carried out various experiments in cutaneous biology, skin pharmacology, and clinical studies that were focused specifically on stretchmark prevention and treatment.

6. I have read the Application and the Office Action dated July 3, 2002, and I acknowledge the Examiner's rejection under Section 112.

7. A few years ago, I discovered an unexpected use for fermented soya peptides or peptides obtained by chemical synthesis, wherein the fermented soya peptides or synthesized peptides are useful for the prevention, reduction, or treatment of stretch marks. The fermented soya peptides or synthesized peptides, optionally may include AHA (Alpha Hydroxy Acid).

A – ACTIVE INGREDIENTS

Fermented Soya peptides are obtained by a specific and patented biotechnological process whereby a selected soya protein is fermented/hydrolysed by microorganisms like *Lactobacillus*. Our supplier of fermented soya peptides, COLETICA (Lyon, France), produces fermented soya peptides by fermenting soya protein in the presence of *Lactobacillus plantarum*, (*i.e.*, Phytokine®). *Lactobacilli* contain a broad spectrum of hydrolytic enzymes, (*i.e.*, proteases), which hydrolyze proteins at numerous sites. These microorganisms also contain modifying enzymes such as glycosylases and phosphorylases. Fermenting a selected soya protein with a particular strain of *Lactobacillus* can produce fermented soya peptides that demonstrate biological activity. However, not all fermented soya peptides demonstrate biological activity. For example, among two hundred fermented soya peptide extracts, (*i.e.*, twenty selected proteins X ten selected microorganisms) evaluated by cell proliferation screening, only one produced by soya protein fermented by *Lactobacillus plantarum* demonstrated a positive result.

The selected fermented peptides stimulate synthesis of extracellular matrix components on an equivalent dermis model (*e.g.*, collagen synthesis increased 65% and hyaluronic acid synthesis increased 68%). When applied on a reconstructed skin model, peptides having an average molecular weight of 800 Daltons penetrated through the skin to the dermis and stimulated the synthesis of macroproteins. (See Annex for additional data on this product, (Phytokine®, COLETICA)). No other fermented peptide produced by a

selected soya protein and microorganism has shown this biological activity. This confirms the real specificity of the selected fermented peptide.

The selected peptides are absolutely different from the soya proteins as disclosed by Ribier *et al.* (US 5,614,215). The soya proteins as disclosed in Ribier *et al.* only have a surface activity on skin (*i.e.*, a tensile effect) because of their high molecular weight, which can explain their smoothing effect on wrinkles (superficial and visual antiaging effect), but they do not have a real biological anti-aging effect. Ribier *et al.* teaches dispersion of soya protein to the deep layers of the skin by lipid vesicles. The fermented soya peptides of the present invention do not require lipid vesicles to penetrate through the skin.

The synthesized peptide of the present invention (*e.g.*, Kollaren-CPP®, SEPORGA/Sophia, Antipoli, France), which is not fermented, is a homologue of the active fraction of collagen I and III precursors and shows very interesting properties in stimulating cutaneous regeneration. For example, the synthesized peptide increases the extensibility of skin and induces an interesting improvement of the biomechanical properties of the skin by the standard method skin-stretching test. This peptide also stimulates collagen III synthesis in fibroblast cultures.

B – CLINICAL STUDIES (Discussion of the prevention, the reduction and the treatment of stretchmarks)

To demonstrate the ability of this invention to have a real benefit on stretchmarks, we performed three clinical studies:

1. A randomized double blind clinical study versus placebo.

The first study was a randomized double blind clinical study versus a placebo. In this study, we evaluated (versus a placebo consisting of an emulsion of oil and water), the potential prevention effect against stretch marks afforded by the topical application (twice daily) of a cosmetic cream containing 10% lactic acid (pH 3.5) and a soya peptide, biofermented by *Lactobacillus*, which had been shown to stimulate the production of all matrix proteins *ex vivo*. Seventy four pregnant women, from the third to fifth month of pregnancy, were included and were followed from T_0 (T =period of application in month) to T_3, T_5 and T_{pp} (1 month post partum). Clinical evaluation by a dermatologist and auto

evaluation by women were performed at each time on 5 criteria including presence, length, width, color, and relief, using an analogous visual scale of 10.

The results at T_5 and T_{pp} demonstrated that the cosmetic cream was efficient versus placebo. Frequency of appearance of stretchmarks decreased by 50%. Stretchmarks were 1.5 times less prominent, 2.0 times less inflamed and red ($p=0.03$), 1.5 times less relief ($p=0.1$), and less long ($p=0.03$). The rate of appearance was also slower ($p<0.05$). Volunteers have quoted a real improvement of hydration, firmness, tonicity, elasticity, and suppleness. These results confirm our previous cutometric and clinical results ($p<0.05$) based on an open treatment of stretch marks post-partum.

Conclusion: The product at least partially prevents the appearance of stretch marks by reducing the frequency of appearance by a factor of two and also prevents the gravity of the scars. These results have been presented at the World Congress of Dermatology in Paris and at the European Academy of Dermatology and Venereology in Prague this year. (See VDA poster in Annex). Finally, a well regarded French Dermatology Publication (Réalités Thérapeutiques en Dermato-Vénérologie n° 122 – Nov. 2002) mentioned our clinical study in its last issue with the title: "Prevention of Stretch Marks: Is It Possible?", and it concluded that "this study confirms the potential interest in the prevention at least partially of stretch marks by this new formula".

2. **Clinical study on the reduction of stretch marks on twenty post-partum female adult volunteers (See Annex: report no. 80297RE – I.E.C. product studied: Vergetures Double Action).**

In the second study, we evaluated the reduction of stretch marks on twenty post-partum female adult volunteers. After three consecutive months of application of a formulation containing fermented soya peptide and AHA on the thighs and abdomen, we confirmed a fairly clear regression of developing post-partum stretch marks (length, width, color and relief), as shown by a statistically significant improvement:

- in skin tonicity and a decrease in its looseness measured by cutometer;
- in width (decrease of 12%), length (decrease of 13%), color (decrease of 24%), and relief (decrease of 27%), as clinically evaluated under dermatological control;

- as compared with initial evaluations and to those recorded on the untreated control area: in suppleness (increase of 12%), elasticity (increase of 19%); length (decrease of 29%), width (decrease of 16%), color (decrease of 39%), relief (decrease of 26%), as evaluated by the panellists on the basis of analogous visual scales. Also, the reduction of post-partum stretchmarks is associated with a very clear effect on the moisturization of the outlayers of the epidermis (increase of 20 to 30%) as determined by electrical capacitance measurements.

3. **Clinical study on the regression of stretch marks on twenty one female adult volunteers. (See Annex: report no. 80296RE – I.E.C. product studied: Vergetures Action Intensive).**

After three months of application of a formulation containing the synthetic peptide and AHA on the thighs, hips, and abdomen under normal conditions of use, we measured a slight regression of stretch marks shown by a statistically significant improvement:

- of skin's elasticity component and a decrease in its fatigability measured using a cutometer (which measures the cutaneous viscoelastic parameters : elasticity, tonicity, firmness).

- in the width (decrease of 7%), color (decrease of 12%) and relief (decrease of 10%) of the stretch marks, with a tendency to decrease in length (decrease of 4%) when evaluated clinically under dermatological control.

- in the skin suppleness (increase of 22%) and elasticity (increase of 32%) and the width (decrease of 8%), color (decrease of 14%), relief (decrease of 16%) of the stretch marks, and the tendency to decrease in length (decrease of 6%), when evaluated by the panellists on the basis of analogue visual scales.

Conclusion of studies 2 and 3: In these two similar clinical studies, we confirmed the the reduction of post-partum stretch marks *in vivo* of the two formulations containing the two peptides (either fermented soya peptides or synthesized peptides) with AHA. These new data confirm the related data in our specification.

C – SUMMARY

Stretchmarks are the result of common skin trauma which is generally due to a distension of the elastic network under physical constraint during pregnancy. Fermented soya peptides or synthesized peptides, optionally with AHA at a very acidic pH, can penetrate deeply through the skin and in particular to the dermis, to stimulate the production of collagen, hyaluronic acid, and other macroproteins. These proteins contribute to the skin's elasticity and ability to resist physical constraint during pregnancy. In the three clinical studies above, we demonstrated that the viscoelastic parameters measured by cutometer were improved so the skin is more tonic and elastic (*i.e.*, the skin could more efficiently resist the physical constraint). We have also confirmed the high moisturizing power of these formulas, which has a very positive effect on the superficial elasticity of skin.

Clinically, these two formulas reduced the formation of stretch marks during pregnancy (50% less frequent versus placebo), and effected a reduction of the clinical score of scars during pregnancy (inflamed, red stretchmarks) or post-partum scars (non inflamed, white stretchmarks).

Moreover, the present invention is non-obvious as evidenced by its commercial success. Several thousands of compositions that contain VDA (composition of Phytokine® and AHA) or VAI (composition of Kollaren-CPP® and AHA), as described and claimed in the present specification, have been sold in the U.S. during year 2002. The attached Table I shows that the projected needs for these compositions for year 2003 will total 466 thousand units = 739 kdollars.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

Epernon, le 24 décembre 2002

Philippe MSIKA

ANNEX 2

See § B page 4 (DECLARATION)

CLINICAL STUDIES – conclusion

VDA POSTERS

VDA Poster

PREVENTION OF STRETCH MARKS / A RANDOMIZED DOUBLE BLIND CLINICAL STUDY *VERSUS* PLACEBO

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INTRODUCTION

Striae distensae, commonly referred to as stretch marks, occur on the abdomen and/or breast in 90% of all pregnant women (striae gravidarum), after the sixth month of pregnancy. They are the result of extrinsic factors (ie, mechanical stress), but more important of intrinsic factors (eg, hormones/steroids, genetic predisposition and physiological stress) that interact to produce these lesions. They are generally 2 to 5 mm in width. During the earliest stages, women may describe minor pruritus or irritation. The lesions are frequently seen over the peri-umbilical area, the thighs, buttocks and breasts. After delivery, they gradually fade in colour and appear as white, atrophic, depressed lesions, often with a wrinkled surface.

Although only partially understood, recent works, with electronic microscopy and immuno-histochemistry, have demonstrated at least three essential factors for the development of striae distensae : cutaneous stretching, hormonal impact and inflammation. These three factors led to the inhibition of collagen and elastic fibers synthesis by dermal fibroblasts and to the induction of collagenases ans elastases (MMP=Matricial Metallo Proteases).The final result is a desorientation of dermal fibers with a re-orientation following the stretching lines and the clinical pseudo-scar aspect.

The following trial involves a marketed product containing 10% lactic acid (pH 3.5) associated with a soya peptide, biofermented by Lactobacillus, which activates the production of all matrix proteins *ex vivo*. The association of an alpha-hydroxy-acid to the soya peptide potentiates its activity and provokes a synergistic effect in preventing and/or treating stretch marks.

MATERIAL AND METHODS

This randomised, double-blind trial *versus* placebo has been conducted under gynecologic and dermatologic control. 74 women have been included, during their third, fourth or fifth month of pregnancy. They randomly received either the patented product (36 women, 22 to 37 years old) or the placebo (emulsion O/W, 38 women, 23 to 39 years old). They applied the tested products (**VDA**) twice daily on the thighs, the hips and the peri-umbilical area until the end of the first month post-delivery.
Evaluations were performed at T0, T+3 months, T+5 months and Tpp (1 month post-partum).
Clinical evaluation by a dermatologist and auto evaluation by women were performed at each time, on 5 criteria : presence, length, width, colour and relief, with an analogic scale in 10 points.
Macrophotographies (Nikon F-801S, 105MM) of the thighs and the peri-umbilical area were achieved at each visit.
Statistical analysis used Wilcoxon test and U test (Mann Whitney).

RESULTS

The results at T+5 and Tpp showed that the patented association was efficient *versus* placebo :

- **New striae distensae (Figure 1)** : The development of stretch marks was largely reduced (-50%) under **VDA** compared to placebo. Their rate of appearance was slower ($p<0.05$) ie, the statistically significant increase of striae distensae number was reached at Tpp under patented product and earlier at T+5 under placebo.

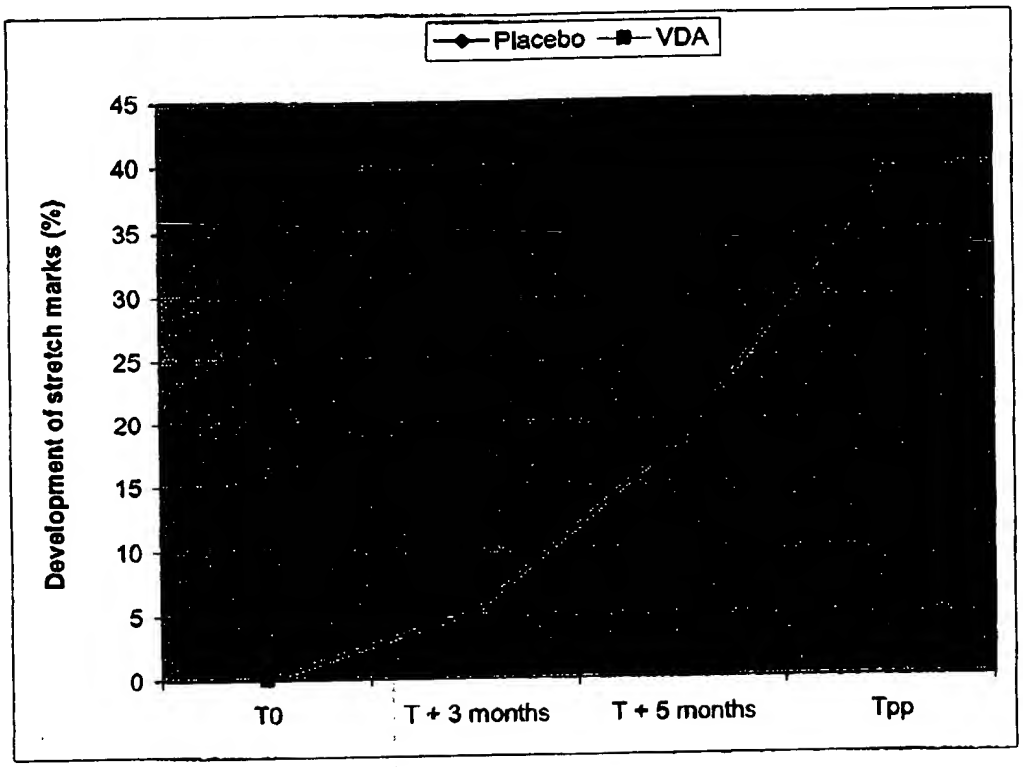
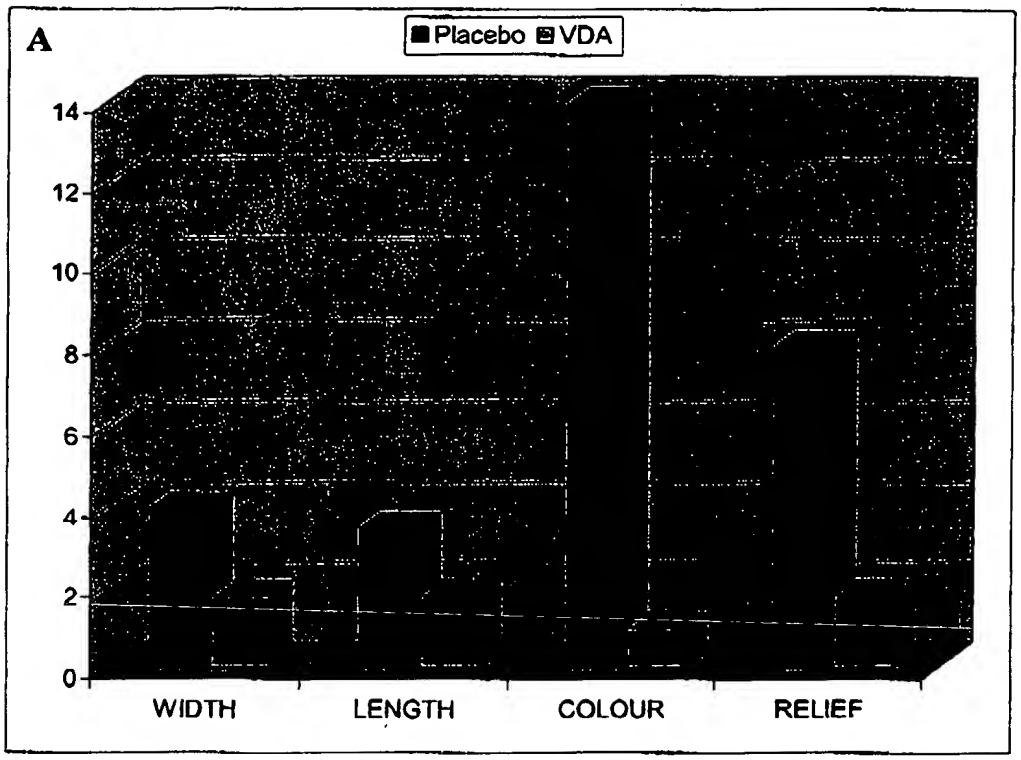


Figure 1 : Compared to the placebo, the twice daily application of VDA reduces by 50% the development of striae distenseae on the abdomen.

- **Clinical dermatologic evaluations (Figures 2, A&B)** : The new stretch marks observed were 1.5 time less important, 2 times less inflamed ($p=0.03$), 2 times less red ($p=0.03$), 1.5 time less reliefed ($p=0.1$) and less long ($p=0.03$).



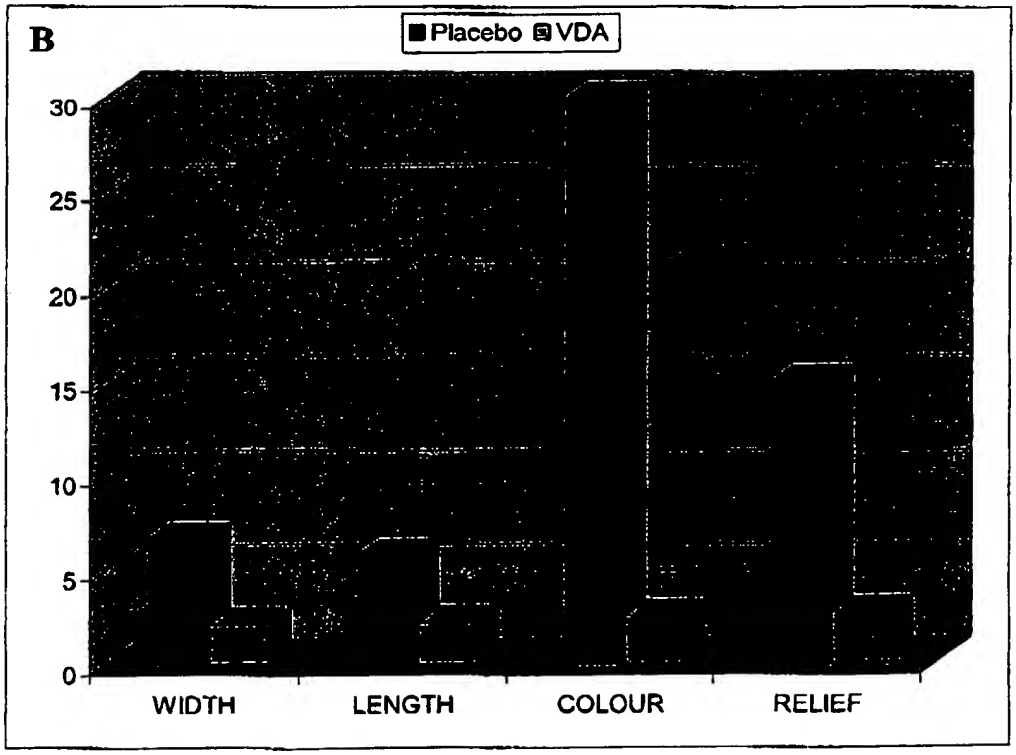


Figure 2 : Evolution of the striae distensae parameters. Dermatological evaluation at T + 5 months (A) and Tpp (B).*Statistically significant compared to placebo.

- **Auto-evaluations (Figure 3)** : Volunteers have noted similar efficacy on stretch-marks about their length, width, colour and relief . They also noted a real improvement of hydration (78% good or very good), firmness (78%), tonicity (86%), elasticity (94%) and suppleness (92%) at T+5.

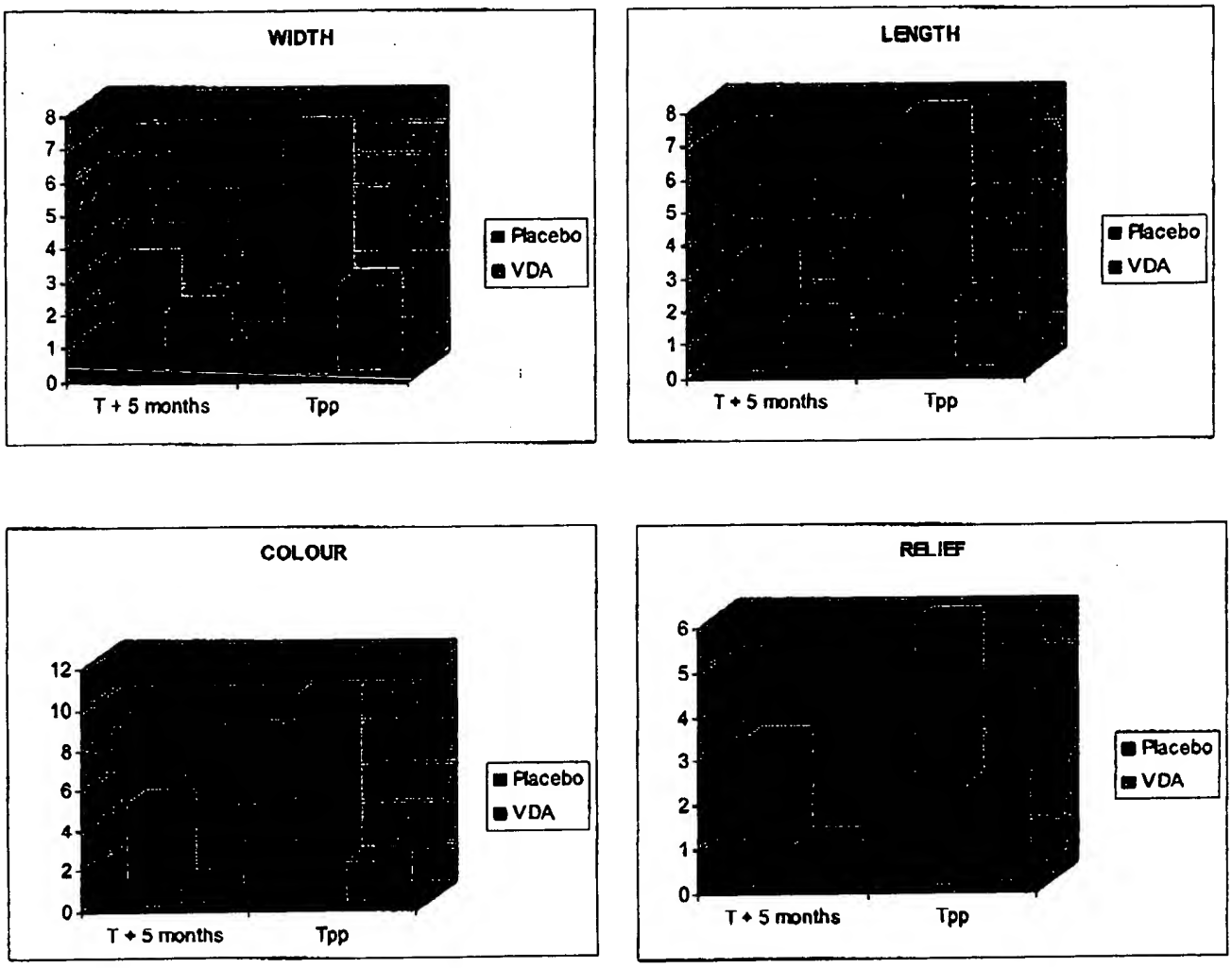


Figure 3 : Clinical evaluation of the stretch marks parameters by the volunteers.

- **Macrophotos** : Here are some characteristic evolutions of striae distensae with **VDA** and with placebo **(Figure 4)**.

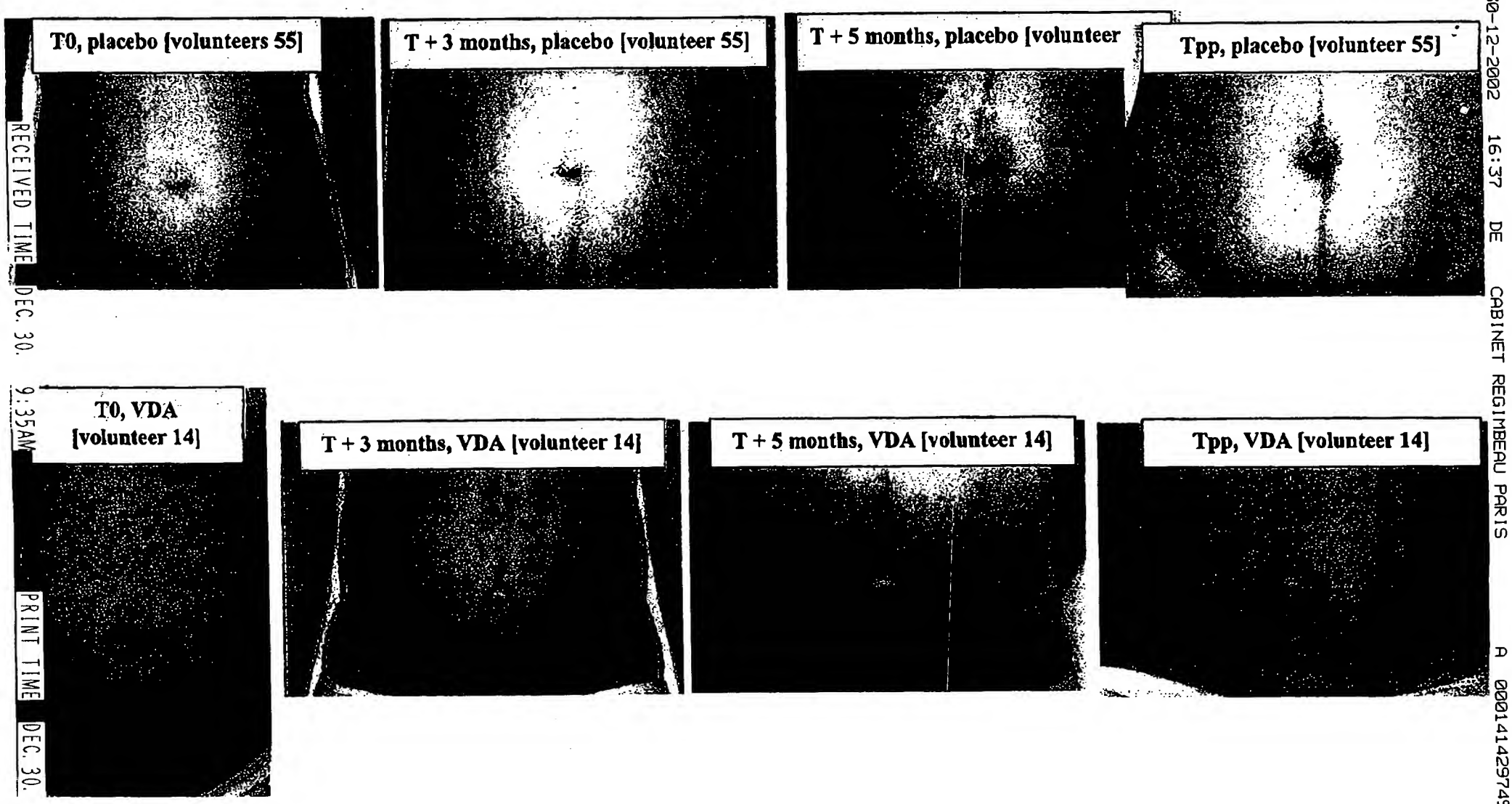


Figure 4 : Illustration of the evolution of the stretch marks for one volunteer using VDA [14] and one volunteer using the placebo [55]. VDA>PLACEBO.

CONCLUSION

Stretch-marks are very common problems during pregnancy and remain very difficult to treat. Prevention is the best way to act, because curative treatment remains deceptive. Retinoic acid has been tested on stria distensae with some results but remains very irritant in the locations of stretch marks (breast, thighs...) and is contre-indicated during pregnancy.
Cosmetic products are numerous but very few have been tested with pertinent clinical assays, ie randomised double-blind studies *versus* placebo. This was the fact with a new patented product containing lactic acid and soya peptides which targets are dermal collagen and elastic fibers. The present study on 73 pregnant women have demonstrated that prevention of stretch-marks during pregnancy is possible : Speed of development is reduced, number divided by 2, lesions less visible because less red and surface less prominent. These performances have been evaluated both by dermatologists and by the volunteers themselves.
The majority of these women have judged that this new product represents an efficient tool against striae distensae. They also positively judged its cosmetic properties : consistence, texture, perfume...
The tolerance has been good to excellent in all cases with no significant difference with the placebo.

REFERENCES

1-Zheng P et al : Br J dermatol 1985, 112 : 185-193
2-P.Nigam :Int J Dermatol 1989, 2,7 :426-428
3-R.Watson et al : Br J Dermatol, 1998, 138 : 931-937
4-T.Tsuji et al : J Cutan Pathol 1988, 15 : 215-222
5-A.Jarrett : J Appl Cosmetol 1989, 7 : 89-91

ANNEX 1

See § A page 3 (DECLARATION)

ACTIVE INGREDIENTS

Phytokine®

PHYTOKINE®

In depth firming action

PLAN

PHYTOKINE®

In depth firming action

SKIN FIRMNESS LOSS PHYSIOLOGICAL ELEMENTS

Dermis and epidermis thickness reduction.

Collagen III / collagen I ratio increase.

PHYTOKINE®

In depth firming action

SKIN FIRMNESS LOSS, PHYSIOLOGICAL ELEMENTS

- Extracellular matrix components synthesis reduction: collagen, GAGs, elastin.
- Collagen reticulation (glycation).

PHYTOKINE®

In depth firming action

Soy extracts

Microorganism (specific enzymatic equipment)

PHYTOKINE®, enzymatically modified peptides

A CELL MESSENGER FROM BIOTECHNOLOGY

Biotechnological modifications:

- Specific cuts
- Enzymatic modifications:
  - Glycosylation
  - Phosphorylation
  - ...

Specific and reproducible biological properties

PHYTOKINE®

In depth firming action

A CELL MESSENGER FROM BIOTECHNOLOGY

Selected among 200 biotechnological extracts, by a cell proliferation screening

- 20 proteins x 10 micro-organisms
- 200 biotechnological extracts

Selective biotechnological modifications

PHYTOKINE®

In depth firming action

BIOLOGICAL ACTIVITIES: EVALUATION ON UNIQUE MODELS

➡ Equivalent dermis

➡ Reconstructed skin

➡ Biopsies (in vivo test)

PHYTOKINE®

In depth firming action

EXTRACELLULAR MATRIX COMPONENTS SYNTHESIS STIMULATION

On equivalent dermis model: collagen synthesis evaluation in absence (reference), and in presence of PHYTOKINE®.

(*) Statistically significant difference from control (Student test P<0,01)

PHYTOKINE®

In depth firming action

EXTRACELLULAR MATRIX COMPONENTS SYNTHESIS STIMULATION

On equivalent dermis model:
chondroitin-4-sulphate (C4S) and hyaluronic acid (HA) synthesis evaluation without (reference), and with PHYTOKINE®.

(*) Statistically significant difference from control (student test P<0.05)
(**) Statistically significant difference from control (student test P<0.01)

PHYTOKINE®

In depth firming action

EXTRACELLULAR MATRIX COMPONENTS SYNTHESIS STIMULATION

On reconstructed skin model: collagen synthesis evaluation without (control), and with PHYTOKINE®

PHYTOKINE®

In depth firming action

EXTRACELLULAR MATRIX COMPONENTS SYNTHESIS STIMULATION

On equivalent skin model: HA Synthesis evaluation without (control), and with PHYTOKINE®

PHYTOKINE®

In depth firming action

EXTRACELLULAR MATRIX COMPONENTS SYNTHESIS STIMULATION

In vivo Study Process

- *Study carried out on 8 volunteers between 42 and 67 years.*
- *The half face treated with a placebo.*
- *The other half face treated with a formula containing 2% PHYTOKINE®.*
- *Application twice a day during 28 days.*
- *Tests on skin biology after lifting.*

PHYTOKINE®

In depth firming action

EXTRACELLULAR MATRIX COMPONENTS SYNTHESIS STIMULATION

In vivo study: parameters

- *Collagen quantity*
- *GAG's quantity*
- *Type III / I collagen ratio variation*

PHYTOKINE®

In depth firming action

EXTRACELLULAR MATRIX COMPONENTS SYNTHESIS STIMULATION

In vivo study: Results

➡ **Collagen quantity.**

PHYTOKINE®

In depth firming action

EXTRACELLULAR MATRIX COMPONENTS SYNTHESIS STIMULATION

In vivo Study: Results

- **GAGs quantity**

PHYTOKINE®

In depth firming action

EXTRACELLULAR MATRIX COMPONENTS SYNTHESIS STIMULATION

In vivo Study: Results

➧ *Type III / I collagen ratio variation*

PHYTOKINE®

In depth firming action

CONCLUSION

- PHYTOKINE® acts efficiently on the synthesis of the essentials components responsible for the skin firmness.
- The original, exclusive, and relevant models (in vitro and in vivo) on which the results were obtained have strongly validated the efficacy of PHYTOKINE®.

PHYTOKINE®

In depth firming action

APPLICATIONS

- Anti-wrinkles restructuring skin care,
- Face and neck anti relaxing skin care,
- Eye contour firming skin care,
- Body remodelling skin care.

PHYTOKINE®

In depth firming action

TOXICOLOGY

- Non-irritating for the skin
- Non-irritating for the eyes
- No abnormal oral toxicity (doses > 5g/kg)
- Hypoallergenic

PHYTOKINE®

In depth firming action

SUMMARY FILE

INCI denomination	Hydrolyzed Soy Protein
Equivalent Japan denomination	Hydrolyzed Soybean Protein (9067-32-7 / 42)
CAS #	68607-88-5
EINECS#	271-770-3
Preservatives/Additives	Microbiocide Colética (1%).
Origin	Produced by fermentation of Soy protein (*Lactobacillus Plantarum*)
Concentration of use	From 1 to 4%
Method of incorporation	Add in the end of formulation at 30°C. Never cold Store.

PHYTOKINE®

In depth firming action

SUMMARY FILE (CONTINUED)

Final Specifications

Dry matter (15 hours, 105°C)	2.1 - 3.0 %
Mineral matter (15 hours, 600°C)	0.3 - 0.6 %
Total proteins (Biuret)	0.4 - 0.8 %
Reducing sugars (DNS method)	0.02 - 0.3 %
Methylparaben (HPLC)	0.04 - 0.07%
Ethylparaben (HPLC)	0.04 - 0.07%
Propylparaben (HPLC)	0.01 - 0.03%
Aspect	Clear, no particles
Superior extreme color	143C + 145 C
Median color	125 C + 129C
Interior extreme Color	125 C + 128 C
pH	5.6 - 6.4
Refractive Index (20°C)	1.33 - 1.35
Number of aerobic micro-organisms (30°C)	≤ 100/g
Pathogenic micro-organisms	None

Cosmetic Properties

- Restoration of cell renewal mechanisms,
- Activation of the synthesis of extracellular matrix components (collagen, elastin),
- Restructuring, regenerating and firming action.

Applications

- Anti-wrinkle, restructuring skin care,
- Face and neck anti-relaxing skin care,
- Face contour firming skin care,
- Body remodelling skin care.

ANNEX 3

See § 2 page 4 (DECLARATION)

Clinical study on the reduction of stretch marks

Report N° 80297RE

INSTITUT D'EXPERTISE CLINIQUE

Head office : route de Bibost, 69690 Bessenay - France
Phone : (33) 4.74.70.93.39 - Fax : (33) 4.74.70.94.98

PROMOTEUR :
Laboratoires PHARMASCIENCE

PRODUIT ETUDIE :
VERGETURES DOUBLE ACTION
(lot n° JD 436-60)

OBJECTIVATION AND CUTANEOUS TOLERANCE STUDY

SUMMARY

PREVENTIVE EFFECT ON STRETCH MARKS

CLINICAL STUDY FOR THE EVALUATION OF THE PREVENTIVE EFFECT OF A COSMETIC TEST ARTICLE ON STRETCH MARKS, AND ASSESSMENT OF ITS GOOD CUTANEOUS TOLERANCE, UNDER DERMATOLOGICAL, PHLEBOLOGICAL AND GYNECOLOGICAL CONTROLS, AFTER REPEATED CUTANEOUS APPLICATIONS, UNDER NORMAL CONDITIONS OF USE, FOR 3 MONTHS, BY 20 (or 19) FEMALE ADULT VOLUNTEERS

STUDY OBJECTIVE

Evaluate the "preventive" effect of a cosmetic product on the stretch marks, by measurements of the electrical capacitance and biomechanical parameters of the skin, combined with assessments, replica and photographs, under Dermatological, Phlebological and Gynecological controls, after repeated cutaneous applications for 3 months, under normal conditions of use, by 20 (or 19) female adult volunteers, from 18 to 35 years old, with "starting, post-partum" stretch marks, dating from less than 3 months, to the thighs or the stomach.

PERTINENCE OF THE ESSAY

. Measurement of cutaneous viscoelastic parameters, by means of a Cutometer™, allow to determine the effect of a cosmetic product on the skin biomechanical properties, after repeated applications. This device measures the deformation of a cutaneous area, submitted to a mechanical suction and its recovering power (Wilhelm and al., 1993). The skin viscoelastic properties are directly correlated to skin suppleness, elasticity, tonicity and firmness.

- The measurement of the skin electrical capacitance (Corneometer-technique) is one of the most widely used method to assess the epidermal outlayer water content and to quantify the moisturising effect of cosmetic or dermatological products (Korstanje and al., 1992 ; Vilaplana and al., 1992 ; Loden and al., 1992). This technique is based on the electric principles described in the following equation :

$$Z = [Rx^2 + (1/2\pi fCx)^2]\ 1/2$$

Z : impedance ; Rx : resistance (Rx = 1/conductance) ; f : frequency ; Cx : capacitance.

Due to the high dielectric constant of water, the electrical characteristics of the stratum corneum depend on its water content and allow investigating the epidermal outlayer moisturisation level (Tagami and al., 1980).
Therefore, repeated measurements of capacitance give the ability to objectively assess the effect of cosmetics on stratum corneum water equilibrium and on the skin moisturisation level, by comparison to an area with no product and to the measurement done before the test articles application.

- Combined with an analysis of silicone replica by video imagery (to determine the standardised parameters of the skin relief, for 10 out of the 20 volunteers), with a self-evaluation made on the basis of analog visual scales by the panellist and with a clinical evaluation on the basis of scores, under Dermatological, Phlebological and Gynecological controls, as well as with a questionnaire adapted to the type of test article, these technics allow to objectively evaluate the efficacy of a cosmetic product on stretch marks, on a selection of 20 (or 19) female adult volunteers, after 3 months of daily use, under normal conditions of use, in comparison to a non treated area.

VOLUNTEERS

34 female volunteers, with "starting, post-partum" stretch marks, dating from less than 3 months, to the thighs and the stomach, were recruited and selected after a general medical examination taking into account the inclusion and non-inclusion criteria, as well as the prohibition and restriction concepts defined in the study protocol : 32 came to I.E.C. on the starting day of the study.

21 panellists were then finally included by the Study Investigator on the basis of a clinical examination specific to the study, performed just before its start, after signature more particularly of the compensation modes form and of the informed consent statement. Two of them gave up during the study, during the first month of application, or between the second and the third month of use (abandons not linked to the test article applications).

Analysis of the results was thus made from a panel of 20 female adult volunteers (or 19 at T 3 months), aged from 19 to 41 years old (average : 26 years old).

PROTOCOL

* Initial instrumental and clinical evaluations :

. The viscoelastic parameters of the skin of both thighs were measured with Cutometer ™ (Courage + Khazaka, Germany) on two diametrically opposed areas, delimited to the right and the left thighs of each one of the volunteers, especifically selectioned and recruited to perform and to objectivate this type of test article (on an area of the stomach for the subjects having no stretch marks to the thighs).
These measurements were taken to an area with stretch marks, as well as to an adjacent area, with no stretch marks ("normal skin"), to each thigh and to the stomach, after locating the areas with a transparent plastic mask provided with anatomic marks.

- The electrical capacitance was measured with a Corneometer™ (Courage + Khazaka electronic GmbH, Germany) on the right and left thighs (area without stretch marks).

These measurements were taken after a rest period of about 20 minutes, in an air-conditionned room where the ambient temperature was kept at 22 ± 2° C and the relative humidity at 50 ± 5%.

. The following judgement criteria were assessed by each volunteer, in presence of the Investigator, on the basis of analog visual scales in 10 points (scales from 0 to 9), on each thigh and on the stomach :

. suppleness,
. elasticity,
. stretch marks (lenght and width),
. colour of the stretch marks,
. relief of the stretch marks.

. The following judgement criteria were assessed under Dermatological and Phlebological controls, on the basis of clinical scores in 9 points (from 1 to 9), on each thigh or on the stomach, for each volunteer :

. stretch marks (lenght and width),
. Colour of the stretch marks;
. relief of the stretch marks.

- Cutaneous replica were performed on a skin area with stretch marks, on each thigh (treated and controled areas), for 10 out of the 20 most representative volunteers.

- Macrophotographs in colour of each thigh (treated and control area) were taken on a skin area with stretch marks (the assessment area), for 10 most representative out of the 20 volunteers. These photographs were taken with a camera Nikon F-801S, equipped with a macro objective Nikon 105MM, under a light of type "daylight" (6500° K).

* Determination of the test article efficacy, after repeated applications :

- Methods of applications : the test article was applied twice a day, for 3 consecutive months, under normal conditions of use, by the panellist himself at home, on the skin of the right or the left thigh and on the stomach (for the concerned volunteers).
In order to standardise to the maximum the study conditions, the last application of the test article was done the day before the measurements (T 1, 2 and 3 months), at I.E.C., in the presence of the personnel of the laboratory.

- Effects on the viscoelastic properties and on the degree of cutaneous moisturisation : the viscoelastic parameters and the electrical capacitance of the skin were determined on the areas (with or without stretch marks), marked off with precision with regard to the first day of the study and according the same principles, for each point of time of the study (T 1, 2 and 3 months). These assessments were done 16 to 24 hours after the last application of the test article at I.E.C., in the presence of the laboratory staff, in order to specifically measure the variations of the cutaneous tissue parameters caused by the repeated uses.

- The electrical capacitance was measured with a Corneometer™ (Courage + Khazaka electronic GmbH, Germany) on the right and left thighs (area without stretch marks).

These measurements were taken after a rest period of about 20 minutes, in an air-conditionned room where the ambient temperature was kept at 22 ± 2° C and the relative humidity at 50 ± 5%.

. The following judgement criteria were assessed by each volunteer, in presence of the Investigator, on the basis of analog visual scales in 10 points (scales from 0 to 9), on each thigh and on the stomach :

. suppleness,
. elasticity,
. stretch marks (lenght and width),
. colour of the stretch marks,
. relief of the stretch marks.

. The following judgement criteria were assessed under Dermatological and Phlebological controls, on the basis of clinical scores in 9 points (from 1 to 9), on each thigh or on the stomach, for each volunteer :

. stretch marks (lenght and width),
. Colour of the stretch marks;
. relief of the stretch marks.

- Cutaneous replica were performed on a skin area with stretch marks, on each thigh (treated and controled areas), for 10 out of the 20 most representative volunteers.

- Macrophotographs in colour of each thigh (treated and control area) were taken on a skin area with stretch marks (the assessment area), for 10 most representative out of the 20 volunteers. These photographs were taken with a camera Nikon F-801S, equipped with a macro objective Nikon 105MM, under a light of type "daylight" (6500° K).

* Determination of the test article efficacy, after repeated applications :

- Methods of applications : the test article was applied twice a day, for 3 consecutive months, under normal conditions of use, by the panellist himself at home, on the skin of the right or the left thigh and on the stomach (for the concerned volunteers).
In order to standardise to the maximum the study conditions, the last application of the test article was done the day before the measurements (T 1, 2 and 3 months), at I.E.C., in the presence of the personnel of the laboratory.

- Effects on the viscoelastic properties and on the degree of cutaneous moisturisation : the viscoelastic parameters and the electrical capacitance of the skin were determined on the areas (with or without stretch marks), marked off with precision with regard to the first day of the study and according the same principles, for each point of time of the study (T 1, 2 and 3 months). These assessments were done 16 to 24 hours after the last application of the test article at I.E.C., in the presence of the laboratory staff, in order to specifically measure the variations of the cutaneous tissue parameters caused by the repeated uses.

- **Clinical assessments and self-assessments** : the judgement criteria initially defined were assessed by the volunteer and by the Investigator, according to the same principles as the ones followed during the initial assessments, for each time point of the study (T 1, 2 and 3 months).

- **Replica and macrophotographs** were taken on the cutaneous area exactly marked off with regard to D1, on each thigh (treated and control sites), by the 10 volunteers selected at D1, after the 3 months of use of the test article.

- **Cutaneous local tolerance** was appraised by the Dermatologist, for each time point of the study (T 1, 2 and 3 months), from cutaneous macroscopic examinations which allowed to observe functional and physical signs linked to the test article.

- **Appraisal of acceptability, efficacy and cosmetic qualities by the volunteer** : the efficacy, acceptability and cosmetic qualities of the test article were appraised, for each time point of the study study (T 1, 2 and 3 months), from a questionnaire adapted to the type of the test article, filled in by the volunteer before his visit to I.E.C. : these answers were completed by a global assessment given in the presence of the Study Director.

*** Analysis and interpretation of the results :**

- <u>Biomechanical parameters</u> :
. Mean values of the viscoelastic parameters were determined, for each time point of the study, on the 2 thighs and on the stomach (areas with and without stretch marks), by the calculation of the mean and of the standard error on the mean of individual data taken on all the panellists.
. The values obtained on each one of the treated areas (with and without stretch marks) were compared to those determined on the corresponding control areas (with and without stretch marks), by a variance analysis (ANOVA, significativity : $p < 0.05$) for each time point of the study.
. The values obtained for each time point of the study (T1, 2 and 3 months) were compared to the initial values, by the paired Student "t" test ("one-tail", significativity : $p < 0.05$), for each one of the treated and control areas (with and without stretch marks).
- A variance analysis (ANOVA, significativity : $p < 0.05$) was done concerning on the one hand, the values obtained for each time point of the study (T0, T1, 2 and 3 months), for each one of the corresponding treated and control areas, and on the other hand concerning the differences calculated between the values obtained on the treated area (with and without stretch marks) and those determined on the corresponding control area (with and without stretch marks). A range test allowed, in case a statistically significant time effect was shown into evidence, to determine the times which were different from each other. The analysis on the differences was also done by the paired Student "t" test ("one-tail", significativity : $p < 0.05$).
. The mean percentages of variation for each one of the assessed parameters, during the study, were calculated, on each cutaneous area, with regard to the initial values and to possible variations registered on the control area, from the mean values obtained for all the panellists.

- <u>Capacitance measurements and parameters of the cutaneous relief</u> :
. The mean values of the electrical capacitance and of the cutaneous relief parameters were determined for each time point of the study (T0, T1, 2 and 3 months) on both thighs (treated and control), by the calculation of the mean and of the standard error on the mean of individual data obtained from all the volunteers.
. The values obtained on the treated area were compared with those obtained on the control thigh, by a variance analysis (ANOVA, significativity : $p < 0.05$) or by the paired Student "t" test ("one-tail", significativity : $p < 0.05$), for each time point of the study.

. The values obtained for each time point of the study (T1, 2 and 3 months) were compared to the initial values, determined before the first application, by a variance analysis (ANOVA, significativity : $p < 0.05$) or by the paired Student "t" test ("one-tail", significativity : $p < 0.05$), for each one of the areas.
. The differences calculated between the values obtained on the treated thigh, after 1, 2 and 3 months of use and the initial values were compared to the differences obtained on the control thigh, by a variance analysis (ANOVA, significativity : $p < 0.05$) or by the paired Student "t" test ("one-tail", significativity : $p < 0.05$).
. A range test allowed, in case a statistically significant time effect was shown into evidence, to determine the times which were different from each other.
. The mean percentages of variation of the parameters assessed during the study were calculated for each cutaneous area, at each time point of the study, with regard to the initial values, from the mean values obtained by all the volunteers.

- Analog visual scales and clinical scores :
. Mean values of the judgement criteria were determined for each time point of the study by calculating the mean and the standard deviation (Sd) of individual data collected from each of the volunteers.
. The values obtained after 1, 2 and 3 months of use were compared to the values determined at the first day of the study (clinical assessments), by the Wilcoxon test ("two-tail", significativity : $p < 0.05$), on each one of the treated and control area.
. A variance analysis (ANOVA, significativity : $p < 0.05$) was done concerning on the one hand, the values obtained for each time point of the study (T0, T1, 2 and 3 months), for each one of the corresponding treated and control areas, and on the other hand concerning the differences calculated between the values obtained on the treated area and those determined on the corresponding control area. A range test (Less Significative Difference test, "L.S.D.") allowed, in case a statistically significant time effect was shown into evidence, to determine the times which were different from each other.
. The mean percentages of variation of each one of the criteria assessed during the test were calculated at each time of assessment, with regard to initial values and to the possible variations registered on the control area, from the mean values obtained for all the panellists.

The synthesis of these analyses and the global appreciation formulated by the volunteers on the efficacy and the acceptability of the test article, allowed interpretation of the results according to the type of test articles and to the effects researched by the Study Monitor.

RESULTS AND CONCLUSION

* **Effect on viscoelastic parameters**

Preliminary statistical analysis showed that the initial values of the biomechanical parameters, were identical on each of the areas without stretch marks (treated and control), while slight differences were identified on areas with stretch marks. Therefore, statistical analysis was based on these differences.
The initial values of the Cutometer™ parameters taken on areas with stretch marks were also statistically different from those assessed on areas without stretch marks, showing looser, less elastic skin on areas with stretch marks.

Result analysis showed in evidence :

+ Treated area without stretch marks :
- a statistically significant decrease in Uf (final length) :
  . 7% at T 2 months, as compared with initial values,
  . approximately 8% to 14%, at T 3 months, as compared with the untreated control area,
- a decrease of about 13% to 20% in Uv/Ue (viscoelasticity rate determining the degree of viscous response with respect to elastic response) at T 1, 2 and 3 months, statistically significant as compared with initial values (no variation with respect to the control area).

+ Treated area with stretch marks :
. a statistically significant decrease of 5% in Uf (final length), at T 1 month, as compared with initial values and those taken on the corresponding control area, as well as at T 3 months, as compared with the untreated control area only,
. a decrease in Uv/Ue (viscoelasticity rate) of 8% to 10%, statistically significant as compared with initial values and/or those taken on the control area, at different assessment times (T1, 2 and 3 months).

-> statistically significant improvement in skin tonicity and decrease in loosening of the skin on treated areas with and without stretch marks.

* **Effect on the degree of skin moisturisation**

A very clear and statistically significant increase in electrical capacitance was found as compared with the control area and initial measurements, after 1, 2 and 3 months of use. The gains of moisturisation obtained as compared with variations measured on the control area (measurements taken approximately 20 hours after the last application at I.E.C.), were approximately :

. **20%** at about T 1 month,
. **21%** at about T 2 months,
. **30%** at about T 3 months.

Conclusion: very clear moisturising effect as for the first month of use.

* **Effect on the cutaneous relief** *(video analysis of silicone replica)*

No statistically significant variation of the skin relief was found after the 3 months of use of the test article.

* Self-assessments by the panellists

Results analysis allowed to show into evidence a statistically significant improvement of each one of the following judgement criteria, after 1, 2 and/or 3 months, as compared with the control area and/or initial evaluations :

	T 1 month		T 2 months		T 3 months	
	Control area	Treated area	Control area	Treated area	Control area	Treated area
Suppleness	-16% (p = 0.0720)	+0% (p = 0.8382)	-14% (p = 0.1194)	+2% ° (p = 0.8629)	-7% (p = 0.2568)	+12% ° (p = 0.0323)
Elasticity	-17% (p = 0.1628)	+15% ° (p = 0.0681)	-13% (p = 0.3979)	+17% ° (p = 0.0807)	-9% (p = 0.1308)	+19% ° (p = 0.0256)
Length of stretch marks (short -> long)	-5% (p = 0.6762)	-18% ° (p = 0.0490)	-15% (p = 0.1355)	-11% (p = 0.3021)	+2% (p = 0.8539)	-27% ° (p = 0.0013)
Width of stretch marks (fine -> wide)	+6% (p = 0.5009)	-14% ° (p = 0.1269)	-4% (p = 0.6526)	-4% (p = 0.6809)	+4% (p = 0.5775)	-16% ° (p = 0.0049)
Colour of stretch marks (normal -> abnormal)	-3% (p = 0.6311)	-25% ° (p = 0.0069)	-26% (p = 0.0089)	-38% (p = 0.0006)	-8% (p = 0.0656)	-39% ° (p = 0.0006)
Relief of stretch marks (normal -> sunken / raised)	+2% (p = 0.8845)	-17% ° (p = 0.0726)	-5% (p = 0.3657)	-19% (p = 0.0368)	+8% (p = 0.1975)	-26% ° (p = 0.0006)

(p = -) : probability p with respect to the initial evaluation (by paired Wilcoxon test, "two-tail", significativity : $p < 0.05$)
° : statistically significant variation as compared with the untreated control area (ANOVA or by paired Wilcoxon test, "two-tail", significativity : $p < 0.05$).

* Clinical assessments by the Investigator

Results analysis showed statistically significant improvement in the following judgement criteria, after 1, 2 and/or 3 months, with respect to the control area and/or initial evaluations :

	T 1 months		T 2 months		T 3 months	
	Control area	Treated area	Control area	Treated area	Control area	Treated area
Length of stretch marks (short -> long)	+6% (p = 0.2059)	+0% (p = 1.0000)	+6% (p = 0.3657)	+0% (p = 0.9511)	-2% (p = 0.6547)	-12% ° (p = 0.0126)
Width of stretch marks (fine -> wide)	-5% (p = 0.5839)	-9% (p = 0.0852)	-5% (p = 0.5405)	-9% (p = 0.1588)	-5% (p = 0.0813)	-13% (p = 0.0080)
Colour of stretch marks (normal -> abnormal)	-13% (p = 0.1542)	-24% (p = 0.0145)	-36% (p = 0.0043)	-36% (p = 0.0002)	-16% (p = 0.0310)	-24% (p = 0.0004)
Relief of stretch marks (normal -> sunken / raised)	-28% (p = 0.0093)	-36% ° (p = 0.0010)	-37% (p = 0.0047)	-42% (p = 0.0003)	-11% (p = 0.0532)	-27% ° (p = 0.0009)

(p = -) : probability p with respect to the initial evaluation (by paired Wilcoxon test, "two-tail", significativity : $p < 0.05$)
° : statistically significant variation as compared with the untreated control area (ANOVA or by paired Wilcoxon test, "two-tail", significativity : $p < 0.05$).

* Assessment of the acceptability, the efficacy and the cosmetic qualities of the test article

From the replies obtained from the panellists, the Investigator was able to ascertain a majority of positive answers, as follows :

Acceptability	-> fairly good to very good	:	95%
Efficacy	-> fairly good to good	:	63%

*: *as a "Stretch mark-prevention cream (Preventive Action)"*

From the responses obtained on a questionnaire from the volunteers, the following conclusions were obtained :

		T 1 month	T 2 months	T 3 months
- Regression of "recent" stretch marks	:	35%	80%	79%
. fairly to very clear effect	:	57%	63%	73%
- Moisturising effect :				
. very slight to slight	:	50%	55%	26%
. clear to very clear	:	35%	45%	68%
- Effect on skin tonicity :				
. very slight to slight	:	50%	50%	47%
. clear to very clear	:	10%	15%	26%
- Effect on skin elasticity :				
. very slight to slight	:	55%	65%	53%
. clear to very clear	:	15%	25%	32%
- Firming effect :				
. very slight to slight	:	30%	40%	26%
. clear to very clear	:	-	10%	21%
- Effect on skin suppleness :				
. slight to very slight	:	65%	60%	42%
. clear to very clear	:	15%	15%	37%
- Effect on skin softness :				
. very slight to slight	:	45%	55%	11%
. clear to very clear	:	35%	40%	74%
- Effect on the colour of stretch marks :				
. very slight to slight	:	30%	40%	47%
. clear to very clear	:	35%	35%	42%
- Smoothing effect :				
. very slight to slight	:	55%	45%	42%
. clear to very clear	:	10%	40%	42%

Most of the volunteers expressed a positive judgement of its cosmetic qualities, and in particular, on its consistency (95% of the panel), penetration (68%), spread (95%), non-stainability (84%) and its smell (95%). 74% of volunteers rated the product "fairly good to very good" from a cosmetic point of view.

It is to be noted that 32% of panellists had already used the type of product studied, and that 50% to 67% of them preferred the test article to their usual product, for its efficacy on the colour and size of the stretch marks, and for its speed of action.

* Tolerance of the cosmetic appraised by the Dermatologist and the volunteer

Results analysis allowed to show into evidence a very good tolerance of the test article for 16 of the 19 panellists participating in the whole study.

The other 3 volunteers reported some discomfort reactions, such as :

. cutaneous pricklings of slight to marked intensity, for two of them, felt the first day, or the first week or use, and accompanied by a slight feeling of local warmth for one of them ;

. slight itching for the third one, felt for a few minutes following application, during the first two days of use.

These manifestations, occurring in panellists using this type of product for the first time (for one of them), and occurring only during initial applications, are fairly frequently observed with this type of product studied under these conditions.

In conclusion, the product called "VERGETURES DOUBLE ACTION (lot n° JD 436-60)", applied for 12 consecutive weeks on the thighs and abdomen, under normal conditions of use, as compared with a control area, by 20 (or 19) female adult volunteers, resulted in a FAIRLY CLEAR REGRESSION of "developing, post partum" stretch marks (length, width, colour and relief) less than 3 months old, as shown by :

. a statistically significant improvement of SKIN TONICITY and a decrease in its LOOSENING, measured using a Cutometer™ ;

. a statistically significant improvement in stretch mark, after 3 months of application :
- . of WIDTH (-12%),
- . of LENGTH (-13%),
- . of COLOUR (-24%),
- . of RELIEF (-27%), clinically evaluated under dermatological, phlebological and gynaecological control ;

. a statistically significant improvement compared with initial evaluations, and to those recorded on the untreated control area, after 1, 2 or 3 months of use, in stretch marks :
- . SUPPLENESS (+12%),
- . ELASTICITY (+19%),
- . LENGTH (-29%),
- . WIDTH (-16%),
- . COLOUR (-39%),
- . RELIEF (-26%), evaluated by the panellists on the basis of analog visual scales.

This effect was associated with a VERY CLEAR EFFECT on the moisturisation of the outlayers of the epidermis (+20 to 30%), determined by electrical capacitance measurements during the first month of application.

Furthermore, a positive judgement for its cosmetic qualities was formulated by the majority of the volunteers with regard to its CONSISTENCY (95% of the panel), PENETRATION (68%), SPREAD (95%), "NON-STAINABILITY" (84%) and its SMELL (95%). 74% of the volunteers judged this product "fairly good to very good" from a cosmetic point of view.

Moreover, the applications of the test article were also, on the whole, WELL TOLERATED.

The claims of type "efficacy and tolerance tested under dermatological-Phlebological and Gynecological control" can thus be justified.

Lyon
8 September 1998

J.P. GUILLOT
Senior Pharmacologist -Toxicologist
I.E.C. Manager

Dr. C. GAVAUD-KENNEDY, M.D.
Dermatologist-Phlebologist
Clinical Investigator

Dr. M. PITIOT, M.D.
Gynecologist
Clinical Investigator

QUALITY CONTROL

This study was conducted in conformity with the standard operating procedures of the Clinical Research Center, the general procedures of I.E.C., the signed protocol and the general principles of the Good Clinical Practices published by I.C.H. (Guideline of 1st March 1996).

The control of the clinical studies which are not included in the application field of the Law Huriet is carried out periodically. It is designed to ensure that all critical phases (test article applications and examinations or measurements) of a particular study type are controlled, at least once per month, for the studies performed during this time period. Dates of these controls and study type concerned are given below.

The results of these controls were reported to the Study Director and to the General Management.

Types of study	Dates of controls	Dates of reports to the Study Director	Dates of reports to the General Management
. Identical study :	3 July 1998	6 July 1998	11 July 1998
. Miscellaneous :	Anti-wrinkle effect : 2 June 1998	3 June 1998	9 June 1998
	Smoothing effect : 8 June 1998	9 June 1998	15 June 1998
	Tensing effect : 22 June 1998	23 June 1998	29 June 1998
	Effect on melanogenesis : 3 July 1998	6 July 1998	11 July 1998

This report has been controlled by I.E.C. Quality Control Unit and is an accurate account of the procedures followed, and accurately records the original raw laboratory data generated in this study.

	Date of control	Date of report to the Study Director	Date of report to the General Management
Report (vs. raw data) :	4 September 1998	4 September 1998	4 September 1998

Signature :

Nicole GUILLOT
Head of Quality Control Department

Date : 8 September 1998

ANNEX 4

See § 3 page 5 (DECLARATION)

Clinical study on the regression of stretch marks

Report N° 80296RE

INSTITUT D'EXPERTISE CLINIQUE

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PROMOTEUR :
Laboratoires PHARMASCIENCE

PRODUIT ETUDIE :
VERGETURES ACTION INTENSIVE
(lot n° JD 421-57)

OBJECTIVATION AND CUTANEOUS TOLERANCE STUDY

SUMMARY

EFFECT ON THE "REGRESSION" OF STRETCH MARKS

CLINICAL STUDY FOR THE EVALUATION OF THE EFFECT OF A COSMETIC TEST ARTICLE, ON THE "REGRESSION" OF STRETCH MARKS AND VERIFICATION OF ITS GOOD CUTANEOUS TOLERANCE, UNDER DERMATOLOGICAL AND GYNECOLOGICAL CONTROLS, AFTER REPEATED CUTANEOUS APPLICATIONS, UNDER NORMAL CONDITIONS OF USE, FOR 3 MONTHS, BY 21 FEMALE ADULT VOLUNTEERS

STUDY OBJECTIVE

Evaluate the effect of a cosmetic product on "regression" of the stretch marks, by measurements of the biomechanical parameters of the skin, combined with a clinical assessment, self-assessments, cutaneous replica and photographs, under Dermatological and Gynecological controls, after repeated cutaneous applications for 3 months, under normal conditions of use, by 21 female adult volunteers, from 18 to 38 years old, with "post-partum" stretch marks, dating from 6 months to 2 years, to the thighs and/or to the hips.

PERTINENCE OF THE ESSAY

. Measurement of cutaneous viscoelastic parameters, by means of a Cutometer™, allows to determine the effect of a cosmetic product on the skin biomechanical properties, after repeated applications. This device measures the deformation of a cutaneous area, submitted to a mechanical suction and its recovering power (Wilhelm and al., 1993). The skin viscoelastic properties are directly correlated to skin suppleness, elasticity, tonicity and firmness.

- Combined with an analysis of silicone replica by video imagery (to determine the standardised parameters of the skin relief, for 10 out of the 21 volunteers), with a self-evaluation made on the basis of analog visual scales by the panellist and with a clinical evaluation on the basis of scores, under Dermatological and Gynecological controls, as well as with a questionnaire adapted to the type of test article, these technics allow to objectively evaluate the efficacy of a cosmetic product on stretch marks, on a selection of 21 female adult volunteers, after 3 months of daily use, under normal conditions of use, in comparison to a non treated area.

VOLUNTEERS

30 female volunteers, with "post-partum" stretch marks (white), dating from 6 months to 2 years were recruited and selected after a general medical examination taking into account the inclusion and non-inclusion criteria, as well as the prohibition and restriction concepts defined in the study protocol : 26 came to I.E.C. on the starting day of the study.

23 panellists were then finally included by the Study Investigator on the basis of a clinical examination specific to the study, performed just before its start, after signature more particularly of the compensation modes form and of the informed consent statement. Two of them gave up during the study (abandons not linked to the test article applications).

Analysis of the results was thus made from a panel of 21 female adult volunteers (or 10 for the analysis of the cutaneous relief), aged from 23 to 36 years old (average : 29 years old) and with "post-partum" stretch marks (white), dating from 6 months to 2 years.

PROTOCOL

*** Initial instrumental and clinical evaluations :**

. **The viscoelastic parameters** of the skin of both thighs or both hips were measured with Cutometer ™ (Courage + Khazaka, Germany) on two diametrically opposed areas, delimited to the thighs or to the right or the left hips of each one of the female adult volunteers, especifically selectioned and recruited to perform and to objectivate this type of test article.
These measurements were taken to an area with stretch marks, as well as to an adjacent area, without stretch marks ("normal skin"), to each thigh, after marking off the areas with a transparent plastic mask provided with anatomic marks.
These measurements were taken after a rest period of about 20 minutes, in an air-conditionned room where the ambient temperature was kept at 22 ± 2° C and the relative humidity at 50 ± 5%.

. **The following judgement criteria** were assessed by **each volunteer**, in presence of the Investigator, on the basis of analog visual scales in 10 points (scales from 0 to 9), on each thigh or on each hip :

- . suppleness,
- . elasticity,
- . stretch marks,
- . colour of the stretch marks,
- . relief of the stretch marks.

. The following judgement criteria were assessed by the Investigator, on the basis of clinical scores in 9 points (from 1 to 9), on each thigh and on each hip, for each volunteer :

. stretch marks,
. colour of the stretch marks,
. relief of the stretch marks.

- Cutaneous replica were performed on a skin area with stretch marks, on each thigh or on each hip (treated and controled areas), for 10 most representative out of the 21 volunteers.

- Macrophotographs in colour of each thigh or of each hip (treated and control area) were taken on a skin area with stretch marks, for 10 most representative out of the 21 volunteers. These photographs were taken with a camera Nikon F-801S, equipped with a macro objective Nikon 105MM, under a light of type "daylight" (6500° K).

* Determination of the test article efficacy, after repeated applications :

- Methods of applications : the test article was applied twice a day, for 3 consecutive months, under normal conditions of use, by the panellist himself at home, on the skin of the thigh, of the left or right hip and on the stomach (for the concerned volunteers).
In order to standardise to the maximum the study conditions, the last application of the test article was done the day before the measurements (T 3 months), as well as at intermediate times (T 1 and T 2 months), at I.E.C., in the presence of the personnel of the laboratory.

- Effects on the viscoelastic properties of the skin (tonicity, firmness, suppleness, elasticity) : the viscoelastic parameters of the skin of both thighs were determined on the areas (with or without stretch marks), marked off with precision with regard to the first day of the study and on the same principle, after the 3 months of application of the test article. This assessment was done 16 to 24 hours after the last application of the test article at I.E.C., by the laboratory staff, in order to specifically measure the variations of the cutaneous tissue parameters caused by the repeated uses.

- Clinical assessments and self-assessments : the judgement criteria initially defined were assessed by the volunteers and by the Investigator, according to the same principles as those followed during the initial assessments, after the 3 months of application.

- Replica and photographs of the cutaneous areas were taken on cutaneous areas exactly marked off with regard to D1, on each thigh or each hip (treated and control sites), by the 10 volunteers selected at D1, after the 3 months of use of the test article.

- Local tolerance of the test article was appraised by the Dermatologist, after the 3 months of application, from cutaneous macroscopic examinations which allowed to observe functional and physical signs linked to the test article.

- The efficacy, the acceptability and the cosmetic qualities of the test article were appraised, after 3 months of application, from a questionnaire adapted to the type of the test article, filled in by the volunteer before his visit to I.E.C. : these answers were completed by a global assessment given in presence of the Investigator.

* **Analysis and interpretation of the results :**

- Biomechanical parameters :

. Mean values of the viscoelastic parameters obtained at T 0 and T 3 months, on both thighs or hips (areas with and without stretch marks), were determined by the calculation of the mean and of the standard error on the mean of individual data taken on all the panellists.

. The values obtained on each one of the treated areas (with and without stretch marks) were compared to those determined on the corresponding control areas (with and without stretch marks), by a variance analysis (ANOVA, significativity : $p < 0.05$) before the first application of the test article, and at time 3 months.

. The values obtained after the 3 months of use were compared to the values determined from the first day of the study (initial values), by the paired Student "t" test ("one-tail", significativity : $p < 0.05$), for each one of the treated and control areas (with and without stretch marks).

- A variance analysis (ANOVA, significativity : $p < 0.05$) done on the differences calculated between the values obtained at T 3 months and the initial values, allowed to compare the treated area (with and without stretch marks) with the corresponding control area.

. The mean percentages of variation for each one of the assessed parameters were calculated, on each cutaneous area after the 3 months of application, with regard to the initial values and in comparison to possible variations registered on the control area, from the mean values obtained for all the panellists.

- Self-assessments, clinical assessment and parameters of the cutaneous relief :

. The mean values of the judgement criteria and the parameters of the cutaneous relief, obtained at each period of the study, were determined by the calculation of the mean and of the Standard Deviation (Sd - for self-assessments and clinical scores) or of the standard error on the mean of values (S.E.M. - cutaneous relief) of individual data obtained for all the volunteers.

. The values obtained on the treated area were compared with those obtained on the control site, by the paired Wilcoxon test ("two-tail", significativity : $p < 0.05$), for the self-assessments and the clinical assessments, or by the paired Student "t" test ("one-tail", significativity : $p < 0.05$), for the parameters of the cutaneous relief.

. The values obtained after 3 months of use were compared to the values determined from the first day of the study (initial values), by the paired Wilcoxon test ("two-tail", significativity : $p < 0.05$), for the self-assessments and the clinical assessments, or by the paired Student "t" test ("one-tail", significativity : $p < 0.05$) for the parameters of the cutaneous relief, for each one of the treated and control areas.

. The differences calculated between the values obtained on the treated thigh, after the 3 months of application and the initial measurements, were compared to those obtained on the control thigh, by a variance analysis (ANOVA, significativity : $p < 0.05$).

. The mean percentages of variation of each one of the parameters assessed after the 3 months of application were calculated with regard to the initial values and to possible variations registered on the control area, from the mean values obtained for all the panellists.

The synthesis of these analyses and the global appreciation formulated by the volunteers on the efficacy and the acceptability of the test article, allowed interpretation of the results according to the type of test articles and to the effects researched by the Study Monitor.

RESULTS AND CONCLUSION

* Effect on biomechanical parameters

Preliminary statistical analysis showed that the initial values of the biomechanical parameter values were identical, on each of the areas without stretch marks, and on each of the areas with stretch marks. Statistically significant differences were found between areas with and without stretch mark(s), showing looser, less elastic skin on areas with stretch marks.

Result analysis allowed to show into evidence the following, after three months of applications, as compared with initial measurements :

- *Area without stretch marks :*
. a statistically significant decrease in Uv/Ue (viscoelasticity rate determining the degree of viscous response compared with elastic response) at T3 months, as compared with the control area, of 9%,
. a stabilisation of Ur/Uf (elastic recovery rate) and of Ua/Uf (recovery rate following strain).

- *Area with stretch marks:*
. a decrease in Uv/Ue (viscoelasticity rate), not significant with regard to the control area, of 5%,
. a decrease in minimum amplitude (-9% to -39%), during the 1st and 3rd strains,
. a very slight increase in Ua/Uf (recovery rate following strain), as compared with the control area,
. a tendency towards an increase in Ur/Uf (elastic recovery rate).

Conclusion: **statistically significant improvement in the skin's ELASTICITY components and a decrease in its fatigability.**

* Effect on skin relief (video analysis of skin replica)

The analysis of the results did not show any improvement in the relief of stretch marks by skin replica analysis.

* Auto-assessments by panellists

Results analysis showed a statistically significant improvement of the following judgement criteria, as compared with the control area and/or initial assessments :

	Control Area	VERGETURES ACTION INTENSIVE (lot n° JD 421-57)
Suppleness	+0% (p = 0.3173)	+22%° (p = 0.0012)
Elasticity	+2% (p = 0.3173)	+32%° (p = 0.0006)
Length of stretch marks (short -> long)	+2% (p = 0.3173)	-6%° (tendency - p = 0.0836)
Width of stretch marks (fine -> wide)	+0% (p = 1.0000)	-8%° (p = 0.0384)
Colour of stretch marks (normal -> abnormal)	+0% (p = 0.3173)	-14%° (p = 0.0167)
Relief of stretch marks (normal -> sunken / raised)	+0% (p = 0.3173)	-16%° (p = 0.0066)

(p = -): probability p compared to the initial assessment (Wilcoxon test, significativity : p < 0.05)

° : statistically significant variation as compared with the untreated control area (ANOVA or by paired WILCOXON test, "two-tail", significativity : p < 0.05).

* Clinical assessments by the Investigator

Results analysis showed a statistically significant improvement in the following judgement criteria, except for the length of stretch marks, as compared with the control area and/or initial assessments :

	Control area	VERGETURES ACTION INTENSIVE (lot n° JD 421-57)
Length of stretch marks (short -> long)	-2% (p = 0.3173)	-4% (tendency - p = 0.0833)
Width of stretch marks (fine -> wide)	0% (p = 1.0000)	-7%° (p = 0.0143)
Colour of stretch marks (normal -> abnormal)	-3% (p = 0.3173)	-12%° (p = 0.0023)
Relief of stretch marks (normal -> sunken / raised)	0% (p = 1.0000)	-10%° (p = 0.0067)

(p = -) : probability p with respect to the initial assessment (Wilcoxon test, significativity : $p < 0.05$)

°: statistically significant variation as compared with the untreated control area (ANOVA, significativity : $p < 0.05$).

* Appraisal of the acceptability, the efficacy and the cosmetic qualities of the test article

From the replies obtained from the panellists, the Investigator was able to ascertain a majority of positive answers, as follows :

Acceptability -> fairly good to very good : 90%
Efficacy -> fairly good to good: : 48%

Furthermore, a positive judgement for its cosmetic qualities was formulated by most of the volunteers (consistency, texture, penetration, spread, smell, non-stainability and massage ability), as well as of its efficacy, in particular :

- sensation of comfort procured to the skin (57%),
- its moisturising (77% of the panel), firming (52%) effects*, tonicity (66%) elasticity (71%), suppleness (67%) and softness (86%) of the skin, as well as the colour of the stretch marks (52%).
- smoother aspect of the skin* (52%).

* *Very slight to very clear effect*

* Tolerance of the cosmetic product appraised by the Dermatologist and the volunteer

Results analysis allowed to show into evidence a very good tolerance of the test article for 20 of the 21 panellists participating in the whole study.

During the last 3 weeks of use, the other volunteer noted to have felt slight cutaneous pricklings for about 10 minutes, 15 minutes after application.

This phenomenon, liminal and isolated, remains without particular signification.

In conclusion, the product called "VERGETURES ACTION INTENSIVE (lot n° JD 421-57)", applied for 3 consecutive months, on the thighs, hips and abdomen, under normal conditions of use, by 21 female adult volunteers with "post-partum" stretch marks dating from 6 months to 2 years, led to a SLIGHT REGRESSION of the stretch marks, with respect to a control area, shown by :

. a statistically significant improvement in the skin's ELASTICITY components and a decrease in its fatigability, measured using a Cutometer ;

. a statistically significant improvement in the WIDTH (-7%), COLOUR (-12%) and RELIEF (-10%) of the stretch marks, with a tendency to decrease in LENGTH (-4%), when evaluated clinically under Dermatological and a Gynecological control ;

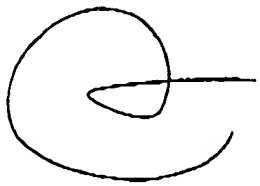
. a statistically significant improvement in the skin's SUPPLENESS (+22%) and ELASTICITY (+32%), as well as the WIDTH (-8%), COLOUR (-14%) and RELIEF (-16%) of the stretch marks, and a tendency to decrease in LENGTH (-6%), when evaluated by the panellists on the basis of analog visual scales.

Furthermore, a positive judgement for its cometic qualities (consistency, texture, penetration, spread, smell, non-staining effect and "massage ability") was formulated by the majority of the volunteers, as well as for its efficacy regarding particularly its MOISTURISING (76% of the panel), FIRMING (67%) effects, as well as TONICITY (67%), and SOFTNESS (86%) procured to the skin. 52% of the volunteers found their skin to be SMOOTHER and 57% appreciated its COMFORT on their skin.

Moreover, the applications of the test article were also, on the whole, WELL TOLERATED.

The claims of type "EFFICACITY AND TOLERANCE TESTED UNDER DERMATOLOGICAL AND GYNECOLOGICAL CONTROL" can thus be justified.

Lyon,
2 September 1998



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QUALITY CONTROL

This study was conducted in conformity with the standard operating procedures of the Clinical Research Center, the general procedures of I.E.C., the signed protocol and the general principles of the Good Clinical Practices published by I.C.H. (Guideline of 1st March 1996).

The control of the clinical studies which are not included in the application field of the Law Huriet is carried out periodically. It is designed to ensure that all critical phases (test article applications and examinations or measurements) of a particular study type are controlled, at least once per month, for the studies performed during this time period. Dates of these controls and study type concerned are given below.

The results of these controls were reported to the Study Director and to the General Management.

Types of study	Dates of controls	Dates of reports to the Study Director	Dates of reports to the General Management
. Identical study :	3 July 1998	6 July 1998	11 July 1998
. Miscellaneous :	S.P.F. :		
	23 June 1998	24 June 1998	30 June 1998
	Anti-aging effect :		
	25 June 1998	26 June 1998	3 July 1998
	P.I. U.V.-A. :		
	8 July 1998	9 July 1998	16 July 1998
	Moisturising effect :		
	10 July 1998	13 July 1998	20 July 1998

This report has been controlled by I.E.C. Quality Control Unit and is an accurate account of the procedures followed, and accurately records the original raw laboratory data generated in this study.

	Date of control	Date of report to the Study Director	Date of report to the General Management
Report (vs. raw data) :	1 September 1998	1 September 1998	1 September 1998

Signature :

Nicole GUILLOT
Head of Quality Control Department

Date : 2 September 1998

ANNEX 5

Table : Sales forecast (volume and turnover)

For year 2003 for the stretch marks products

FORECAST FOR 2003 - EUROPE (SWITZERLAND) AND USA (STRETCHMARKS MARKET)

(Volume and value)

VOLUME 2003 (thousand units)								
	Italy	Spain	Portugal	France	Belgium	Switzerland	USA	total vol.
VDA 200 (lot x2)	7	12	30	200	24	5	31	309
VDA (Pres. Box)	3	7	13	50	3	1	7	84
total VDA	**10**	**19**	**43**	**250**	**27**	**6**	**38**	**393**
VAI	3	3	5	50	4	1	7	73
Total Volume	**13**	**22**	**48**	**300**	**31**	**7**	**45**	**466**

	TURNOVER 2003 (keuros)					total (kEuros	in kCHF	in kDollars
	Italy	Spain	Portugal	France	Belgium	Europe	Switzerland	USA
VDA 200 (lot x 2)	76	125	314	2419	195	3129	95	507
VDA (Pres. Box)	25	52	111	387	21	596	12	107
total VDA	**101**	**177**	**425**	**2806**	**216**	**3725**	**107**	**614**
VAI	34	31	53	503	34	655	13	125
Total Volume	**135**	**208**	**478**	**3309**	**250**	**4380**	**120**	**739**

Gluconate de lithium et dermatite séborrhéique : deux essais français

Chez des patients ayant une dermatite séborrhéique faciale modérée à sévère, on a comparé le gluconate de lithium au placebo et au kétoconazole, avec comme critère principal la guérison complète de l'érythème et de la desquamation après deux mois de traitement.

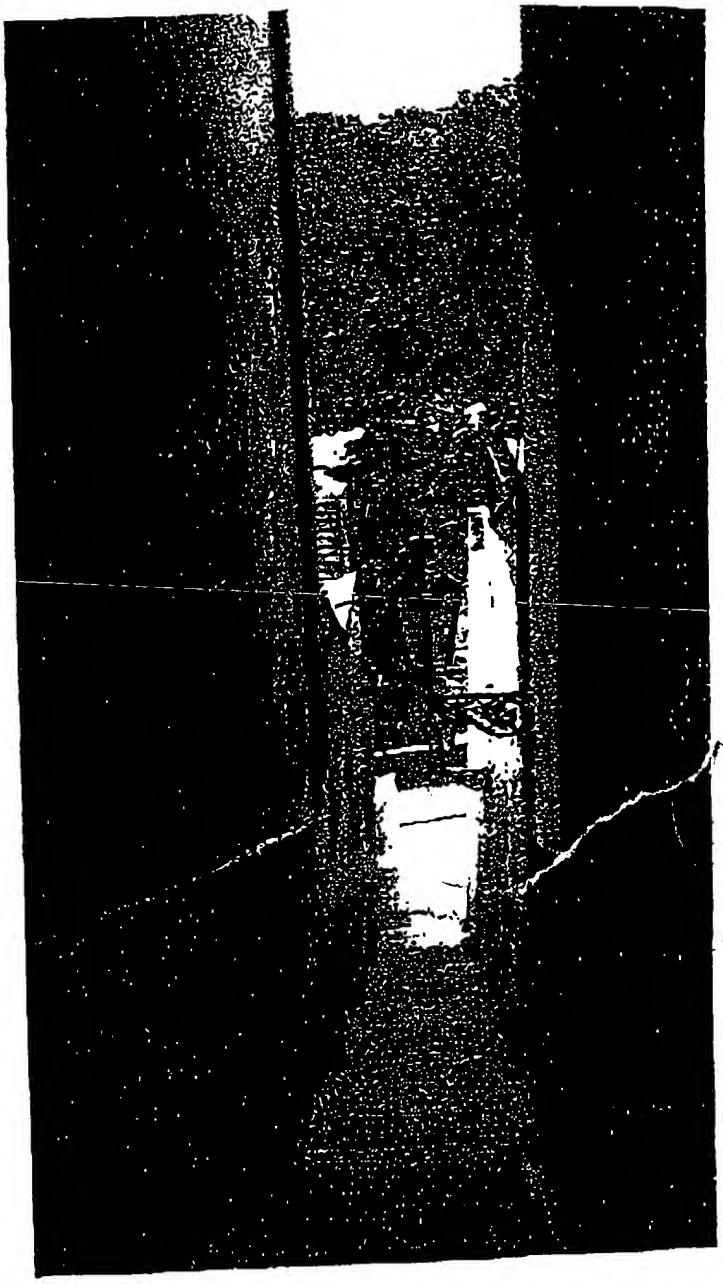
La supériorité vis-à-vis de l'excipient et la non-infériorité par rapport au kétoconazole ont pu être démontrées. Une rémission complète a été obtenue chez 30,7 % des patients sous kétoconazole, *vs* 53,2 % sous lithium, ce qui montre en plus que le lithium est significativement plus efficace que le produit de référence.

On entend parler de ce topique depuis un certain temps déjà et il a pu montrer, comme c'est le cas aussi pour la crème ciclopiroxolamine, une meilleure efficacité que le kétoconazole.

Prévention des vergetures : est-ce possible ?

Un essai français présenté par Pharmasciences fait état d'une étude utilisant un topique contenant 10 % d'acide lactique et un extrait de peptide de soja, biofermenté par des lactobacilles. Il semble que ce produit soit capable d'activer la production de métalloprotéases matricielles, au moins *in vitro*.

L'essai en question a consisté à appliquer deux fois par jour ce topique ou une émulsion huile dans l'eau placebo à partir du 3e/5e mois de grossesse. Au total, 74 femmes enceintes ont été incluses et suivies jusqu'à 1 mois après l'accouchement. Le résultat final montre une diminution de 50 % de la fréquence d'apparition des vergetures. De plus, les vergetures étaient deux fois moins inflammatoires, moins longues et moins profondes. Des résultats antérieurs avaient montré une amélioration de l'apparence en post-partum, et cette étude confirme l'intérêt potentiel dans la prévention au moins partielle des vergetures.



Dermatite péri-orale, tic de léchage des lèvres et adapalène

Un cas est décrit par JANSEN et coll., de la célèbre équipe munichoise. Il s'agissait d'une fillette de 10 ans qui a fini par admettre qu'elle avait l'habitude de se lécher les lèvres (hors de la présence des parents). Après lui avoir demandé de stopper complètement sa mauvaise habitude et d'appliquer de la crème au métronidazole à 2 %, les auteurs ont noté une guérison complète en 3 semaines. Ces tics nécessitent parfois une psychothérapie.

Dans la dermatite péri-orale toujours, une observation isolée de la même équipe suggère que l'adapalène en gel sans aucun autre traitement pourrait être efficace, en association avec l'arrêt de tout topique hydratant et du maquillage.